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Inflammatory Protein Levels and Depression Screening After Coronary Stenting Predict Major Adverse Coronary Events

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Abstract

Background—Traditional risk factors cannot account for the majority of future major adverse coronary events (MACE) in patients diagnosed with heart disease. We examined levels of inflammatory proteins to be possible predictors of future MACE and physiological and psychological factors that initiate temporal increases in inflammatory protein levels.

Methods—Peripheral blood samples and depression data were collected 4 to 12 hr after elective coronary stent insertion in 490 patients. Depression screening was assessed by a single-question screening tool. Predictive modeling for future MACE was performed by using survival analysis, with time from the index event (placement of the stent) to future MACE as the dependent variable.

Results—Patients with high-sensitivity c-reactive protein (hsCRP) in the second and third quartiles were 3 and 2.5 times more likely to have a MACE than patients with hsCRP in the first quartile, respectively. As levels of vascular cell adhesion molecule and monocyte chemoattractant protein-1 increased, so did the risk of future MACE. Patients who screened positive for depression were approximately 2 times more likely to have a MACE within 24 months after stent placement than were patients who did not screen positive.

Conclusions—Our results suggest that hsCRP, vascular cell adhesion molecule, and monocyte chemoattractant protein-1 levels, measured after coronary stent insertion in patients with coronary heart disease, are prognostic of future MACE. Furthermore, positive depression screening is an independent predictor of future MACE.

Keywords

depression; inflammation; cardiovascular outcome; inflammatory proteins; coronary stents

More than 13 million Americans have a history of coronary heart disease (CHD), myocardial infarction (MI), congestive heart failure (CHF), or angina. Determining which of these patients will have future major adverse coronary events (MACE) is difficult (Kini et al., 2003). The risk of future MACE is currently determined by a combination of tests and traditional risk factors (Pearson, 2002) that include measuring left ventricular function, assessing angiographic findings, examining for the presence of ischemia (Kulick & Rahimtoola, 1991; Naqvi et al., 1997), lipid levels, age, gender, race, smoking status, diabetes, and blood pressure. All these

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risk factors combined do not account for all future MACE. Additional risk factors, such as inflammation, are being considered to determine which patients are at increased risk of future MACE.

Studies show temporal increases in levels of inflammatory proteins are prognostic of future MACE (Liuzzo et al., 1998; Mann, 2003). Furthermore, these increases in protein levels can be initiated by both psychological (Bunker et al., 2003) and physiological (Angiolillo et al., 2004) factors. Depressed individuals have been shown to have increased peripheral blood levels of inflammatory proteins such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), c-reactive protein (CRP), (Danner, Kasl, Abramson, & Vaccarino, 2003) monocyte chemoattractant protein-1 (MCP-1), intracellular adhesion molecule-1 (ICAM-1), and E-selectin (Raison et al., 2006). A cross-sectional study of 2,716 acute coronary syndrome (ACS) participants in the Epidemiological Study of Acute Coronary Syndromes and the Pathophysiology of Emotions found that ICAM-1 and IL-6 levels were significantly higher in those with major depression ($p = .002$; depression determined according to the Structured Clinical Interview [SCID] for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV]) than in nondepressed patients ($F = 9.18$, $df = 1,477$, $p = .003$) with a effect size (Cohen's d) = .559 (Lesperance, Frasere-Smith, Theroux, & Irwin, 2004). This seminal observation suggested a role for inflammation in the link between depression and ACS. When increased in patients with CHD, any of these proteins may initiate an inflammatory cascade that could contribute to the instability and rupture of atherosclerotic plaque (Ridker et al., 1997). These increases may result in subsequent MACE (Gidron, Gilutz, Berger, & Huleihel, 2002; Figure 1). Depression stimulates the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis (the system in the adrenal gland and brain that coordinates the body's response to stress). This activity increases levels of catecholamines that activate peripheral macrophages to produce inflammatory proteins (Kini et al., 2003) and corticosteroids that enhance expression of inflammatory protein receptors on endothelial cells (Mortensen, 2001), thereby increasing recruitment, adhesion, and migration of monocytes into the coronary arteries. Higher circulating levels of systemic inflammatory proteins also increase expression of adhesion molecules (ICAM, vascular cell adhesion molecule [VCAM], E-selectin, and P-selectin) and MCP-1. These proteins facilitate the adhesion and transmigration of systemic monocytes across the endothelium (Nelken, Coughlin, Gordon, & Wilcox, 1991). Once inside the coronary plaque, monocytes become macrophages, which further stimulate inflammation in the plaque by releasing IL-1, TNF α , IL-6, MCP-1, and matrix metalloproteinase (MMP; Figure 1).

MMP-1 degrades the extracellular matrix of coronary plaque (Galis, Sukhova, Kranzhofer, Clark, & Libby, 1995), which is already weak from the stresses of biomechanical and hemodynamic forces. Together, the local inflammation and the MMP-1-related plaque degradation cause the plaque to rupture, producing thrombi that block the coronary vessel to cause ACS (Pasterkamp & Falk, 2000). These important recent findings support and extend Lesperance and Frasere-Smith's concept (Lesperance et al., 2004) that transient increases of inflammatory protein levels activated by depression are sufficient to initiate an inflammatory cascade that could contribute to the instability and rupture of a moderate atherosclerotic plaque in individuals with ACS, resulting in subsequent MACE (Gidron et al., 2002; Mann, 2003). In addition, clinical interventions, such as placement of coronary stents that mechanically disrupt and rupture coronary plaque, may initiate an inflammatory response (Gogo et al., 2005; Sanchez-Margalet et al., 2002).

The purpose of this study was to examine the predictive value of a panel of 8 inflammatory proteins, which are increased in both depression and heart disease, and depression screening on time to future MACE after stent placement. First, we will quantify the inflammatory response of patients undergoing coronary stent placement and determine if the level of response

is predictive of future MACE. Second, we will examine whether depression screening is predictive of future MACE. Finally, we will examine the relationship of circulating inflammatory protein levels and depression on subsequent MACE. Our hypothesis is that influence of depression on risk of subsequent MACE is mediated by inflammatory protein levels. We assessed these factors, while controlling for traditional and clinical CHD risk factors, in patients with coronary artery disease who underwent nonemergent stent placement in a native coronary lesion.

Method

Patient Information/Study Design

This prospective, observational study was approved by the University of Texas and the St. Luke's Episcopal Hospital Institutional Review Boards, and written informed consent was obtained from each participant. We enrolled patients with coronary artery disease who successfully underwent nonemergent stent placement in a native coronary artery lesion between September 1, 2001 and September 30, 2003. The research nurses interviewed consenting patients on general health status, cardiovascular risk factors, and personal and family cardiovascular health history, and drew blood samples. A Spanish language consent form and interpreter were used for Spanish-speaking patients. Interview data were validated by chart review.

Inclusion/Exclusion Criteria

Inclusion criteria included successful stenting in a native coronary that was defined as less than 30% residual stenosis in the stented coronary artery, the absence of MACE during the stenting procedure, and successful discharge from the coronary catheterization laboratory. Patients who had more than one stent inserted and other vessels treated during this coronary intervention were included in the study. Because patients with ruptured coronary plaque who have coronary stents inserted have higher levels of inflammatory proteins than those initiated by coronary stent insertion alone, patients with ACS, MI, or unstable angina were excluded from the study. In addition, patients with a malignancy, end-stage renal disease requiring dialysis, and a local or systemic/chronic infection were excluded because these processes result in increased inflammatory protein levels.

Clinical data available from THIRDBase, the Texas Heart Institute's database on cardiac patients undergoing procedures, were used for analysis and to validate patient health status and medical history for study inclusion and study outcomes. THIRDBase data related to this hospital stay included admission and discharge diagnosis, cardiac catheterization procedures, and clinical risk factors (diabetes, hyperlipidemia, hypertension, and smoking status) that affect inflammatory protein levels. We also obtained annual data on postcoronary MACE outcomes of future hospital stays in patients receiving coronary stents (previous history of angina, prior MI, multivessel disease, number of stents, prior percutaneous cardiovascular interventions [PCI] in the target lesion, postprocedure stenosis, CHF, lesion type, and age). The Texas Heart Institute (THI) has a long history of participation in preclinical evaluations, early clinical trials, and long-term outcome studies. Clinical data are abstracted from hospital medical records and entered into the THIRDBase at hospital discharge by a group of trained internally supervised abstracters. THIRDBase has systems in place to ensure reliability of the data, including range edits limits for every data field, consistency checks between fields, and period inter-rater reliability.

Sample Size

Sample size determination for a fixed sample size was calculated using PASS sample size determination for Cox regression analysis based on a 30% event rate of future MACE. A sample

size of 490 patients allowed a power of 80%, event rate of 30%, 2-sided α of .05, β of .20, and a hazard ratio of 1.24.

Instrumentation

Patient interviews were conducted and venous peripheral blood samples were obtained 4 to 12 hr after insertion of the coronary stent. Depression screening was conducted by answering “yes” or “no” to a single question: “Have you felt sad or depressed much of the time in the past year?” The question, first used on 969 primary care patients, performed similarly when compared with the Epidemiological Studies Depression Questionnaire (sensitivity, 85% and 88%; specificity, 66% and 75%, respectively; Williams et al., 1999). With 85% sensitivity and 65% specificity, 85 out of 100 individuals who are depressed will be detected through a positive test, and 65 out of 100 will be correctly screened as not being depressed. Asking about depression over a 1-year time period makes the question more sensitive in screening for prior depressive symptoms. A similar question used to screen for depression in cardiovascular patients had 86% sensitivity and 78% specificity (Watkins, Daniels, Jack, Dickinson, & van Den Broek, 2001). Expert groups in cardiovascular disease in Europe (Albus, Jordan, & Herrmann-Lingen, 2004) and the United States (Group, 2005) have advocated the use of 1 or 2 interview questions to screen for depression in cardiovascular patients. Most clinical instruments that measure depression have about 80% to 90% sensitivity and 70% to 80% specificity (“Screening for depression: Recommendations and rationale”). We chose to use a 1-question technique for screening to decrease patient burden, which involves a detailed history interview during hospitalization.

Stable angina was defined as non-ST elevation on electrocardiogram, normal troponin levels, positive exercise stress test, and chest pain on exertion. Angina was classified according to the Canadian Cardiovascular Society classification scheme. Classification I is when ordinary physical activity does not cause angina, but strenuous or prolonged activity does. Classification II indicates a slight limitation on daily activities (e.g., when rapidly walking or climbing stairs causes angina). Classification III includes marked limitations of ordinary physical activity (e.g., when walking one or two blocks on level at a normal pace causes angina). Classification IV indicates physical discomfort with any physical activity. The lesion was categorized according to American College of Cardiology/American Heart Association criteria (Moushmouth, Kramer, Hsieh, & Klein, 1992) and designated as type A (simple), type B (moderate), or type C (complex). Successful stenting was defined as less than 30% residual stenosis in the stented coronary artery and the absence of MACE during the stenting procedure.

Outcomes

The study outcome, MACE, was defined as cardiovascular death, MI, angina, restenosis, or stroke.

Follow-up

Annual follow-up letters were sent to all participants. Phone calls were made to participants who did not return the follow-up letters. During weekdays, the telephone interviewer contacted study participants at home during working hours and at optimal times (6:00 p.m. to 8:00 p.m.) in the late afternoon and evening unless the patient requested to be called at a specific later time. On weekends, phone calls were made in the mornings from 10:00 a.m. to 12:30 p.m. and in the afternoon from 2:00 p.m. to 7:00 p.m. Participants who moved or were lost to follow-up were traced using family members, friends, and employers’ phone numbers obtained from patients at study entry or from other local sources of information such as the telephone directory, internet search engines (e.g., white pages), and directory information.

Laboratory Methods

The plasma and the white blood cell layer of each blood sample were separated and stored at -80°C . Levels of inflammatory proteins were measured at the Baylor Atherosclerosis Clinical Research Laboratory. The Atherosclerosis Clinical Research Laboratory, located in the Texas Medical Center, measured the inflammatory proteins. Both the College of American Pathologists (CAP) and the Clinical Laboratory Improvement Amendments (CLIA) accredit the Atherosclerosis Clinical Research Laboratory. The laboratory has its own Quality Assurance Plan that meets National Committee for Clinical Laboratory Standards guidelines, as well as those of Baylor College of Medicine and the State of Texas. Commercially available standardized human ELISAs (R and D) were used to measure the blood levels of each of the following inflammatory proteins: E-selectin, IL-6, interstitial collagenase MMP-1, ICAM-1, MCP-1, TNF- α , and VCAM-1. We assessed CRP levels by the immunoturbidimetric CRP-Latex (II) high-sensitivity assay from Denka Seiken (Tokyo, Japan) performed according to the manufacturer's protocol and using a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN).

Analytic Methods

Predictive modeling for future MACE was performed by using survival analysis, with time from the index event (placement of the stent) to future MACE as the dependent variable. Age was analyzed as a continuous variable. Scaled Schoenfeld Residuals were used to validate the proportional hazards assumption of the independent variables and time to MACE. Because the proportional hazards assumption for the inflammatory proteins did not hold, inflammatory protein levels were converted to categorical variables by using quartiles.

Categorical risk factors with a log-rank statistic or continuous variables with a Wald statistic p value less than .25 in the single variable analysis were entered as potential predictive factors of MACE in the multivariable model. Although not statistically significant in the single variable analysis, age was included in the Cox model because of increased absolute risk with aging (D'Agostino, Kannel, Belanger, & Sytkowski, 1989). The adjusted hazard ratio was used to determine the association of each independent variable and the time to MACE, after adjusting for the effects of all the other covariates.

Results

In this study, 490 patients underwent successful elective placement of a stent in a native coronary artery lesion and provided blood samples after the intervention. Serum volume was inadequate for the laboratory measurements in 10 of the 490 samples. The median follow-up period was 24 months. Of the 490 patients who were entered into the model, 400 participants were censored, which means they did not experience a MACE before the study ended or they withdrew from the study. The rate of future MACE for the total sample was 16% (80 patients). The lost to follow-up rate was 20% (98 patients).

The mean age ($\pm SD$) of patients was 65 ± 10.2 years. Most of the patients were white (81%), non-diabetic (69%), men (74%), who were nonsmokers (88%), who had hypertension (80%) and hyperlipidemia (74%). One hundred and nineteen (24%) of the patients had a history of a previous MI. Approximately 18% of the sample ($n = 86$) screened positive for depression. Greater numbers of depression occurred with female gender, other race, CHF, and type B (moderate) and type C (complex) lesions, and higher levels of CRP, ICAM, TNF, ICAM, E-selectin, and MCP-1. Of these, gender ($p = .00001$), CRP ($p = .001$), ICAM ($p = .017$), and MMP-1 ($p = .037$) were statistically significant using univariate analysis. Using multiple logistic regression, only gender was significantly associated with depression ($p = .0001$). Females were 2.84 times more likely to be depressed than males.

To assess potential relationships between MACE and inflammatory protein levels, interquartile ranges were calculated for each protein. Cox regression showed that 12 risk factors in the single variable analysis had significant hazard ratios at a p -value of less than .25 (Table 1). All inflammatory proteins examined in this study, except for E-selectin, were significant predictors of MACE in the single variable analysis (Table 1). At increased risk of MACE were patients with high-sensitivity c-reactive protein (hsCRP) levels of 2.0 mg/dL or greater; ICAM levels of 253.57 ng/mL or greater; TNF- α levels of 0.78 pg/mL or greater; VCAM-1 levels of 471.76 ng/mL or greater; MCP-1 levels of 106.56 pg/mL or greater; and MMP-1 levels of 0.16 ng/mL or greater. These risk factors were entered into the multivariable proportional hazards model.

In the Cox proportional hazards model (Table 1), 8 factors had hazard ratios that were statistically significant ($p = .05$), indicating these factors were independent risk factors for time to future MACE. Patients with diabetes were twice as likely to develop MACE than were non-diabetic patients. In addition, patients who answered yes to the question “Have you felt sad or depressed much of the time in the past year?” were almost twice as likely to develop MACE in 24 months than were patients who answered no to the question. Patients with hsCRP levels in the second quartile were 3 times more likely to have a MACE than those in the first quartile, and patients in the third quartile were 2.6 times more likely to have a MACE than patients with hsCRP in the first quartile. This same trend was seen with VCAM and MCP-1. Patients with levels of VCAM-1 in the third quartile were 3.5 times more likely to experience a MACE than patients with VCAM-1 levels in the first quartile. Patients with MCP-1 levels in the second, third, and fourth quartiles were 4, 3, and 3.6 times more likely, respectively, to have future MACE in 24 months than were patients in the first quartile.

When we removed inflammatory proteins from the analysis in this study, depression was of greater significance ($p = .0176$) in predicting MACE.

Discussion

In this 2-year prospective study of 490 patients with angina, we investigated the prognostic value of a panel of inflammatory proteins and depression screening on time to future MACE, while controlling for traditional and clinical risk factors, such as lesion type and postprocedure stenosis known to influence MACE. Our results indicate that a positive depression screening and increased levels of the inflammatory proteins, hsCRP, VCAM-1, and MCP-1 (along with the traditional risk factor of diabetes) are prognostic of future MACE in patients with stable angina who undergo successful placement of a coronary stent in a native coronary artery lesion. These results support previous reports that depression and levels of hsCRP, MCP-1, and VCAM-1 after stent placement are predictive of future MACE (Gaspardone et al., 1998; Kozinski et al., 2005). These findings can be generalized to patients who undergo elective coronary stent placement in a native coronary artery.

Several clinical trials have assessed the relationship of circulating levels of hsCRP and MACE. Increased levels of hsCRP after stent placement have been shown to predict MACE 1 year after stenting in patients with chronic stable angina pectoris ($n = 81$) who had 1-vessel coronary artery disease and normal levels of hsCRP before stent placement (Gaspardone et al., 1998). In another study, patients with stable or unstable angina ($n = 483$) and hsCRP levels >0.68 mg/dL before stent placement ($p < .001$) were at significantly increased risk of MACE for up to 3 years after stenting (Zairis et al., 2002). In contrast, 2 other prospective studies found no prognostic relationship between hsCRP and future MACE (Gomma et al., 2004; Qi, Li, & Li, 2003). One reason for the disparity in results among studies is the follow-up periods; studies with a longer follow-up period (our study Zairis et al.) show a positive relationship, whereas studies with a shorter follow-up period (Gomma et al.; Qi et al., 2003) show no relationship.

Studies have shown a link between increased circulating levels of VCAM-1 and coronary plaque rupture. In a prospective study of patients with angiographically documented CHD, increased levels of VCAM-1 (1932 versus 1128 ng/mL; $p < .0001$) before coronary angiography were associated with future cardiovascular-related death. Patients within the top quartile of baseline VCAM-1 had a 2.1-fold (1.1 to 4.0) higher risk of death than did patients with VCAM levels in the lower quartiles (Blankenberg et al., 2001). Although our quartile settings were different from those in the above study, our results also indicate that patients with levels of VCAM-1 in the upper quartiles are at a higher risk of future MACE than are patients with VCAM-1 levels in the lower quartiles.

MCP-1, another important mediator of inflammatory response in coronary plaque, is associated with MACE. High levels of MCP-1 after stent placement in patients with stable angina are predictive of time to future MACE in a previous study (Oshima et al., 2001). Our results support these previous findings; however, the previous study had a small sample size ($n = 41$), and exclusion criteria did not include physical factors like chronic or acute infections, which may increase inflammatory protein levels in some patients.

In addition to several inflammatory proteins, our study indicates that a positive depression screen is an independent predictor of time to future MACE after coronary stent insertion in patients with stable angina. In previous studies designed to measure the predictive ability of depression on MACE, major depression was an independent predictor of 6-month cardiovascular death in patients with ACS (adjusted hazard ratio, 4.29; 95% confidence interval [CI], 3.14 to 5.44; $p = .013$; Frasure-Smith, Lesperance, & Talajic, 1993), and ACS patients with major depression were about 3 to 4 times as likely to die within 18 months of discharge as compared with ACS patients without major depression (odds ratio, 3.64; 95% CI, 1.32 to 10.05; $p = .012$; Frasure-Smith, Lesperance, & Talajic, 1995).

Even mild symptoms of depression assessed at one time point by the Beck Depression Inventory in hospitalized patients with unstable angina predicted 5-year mortality ($RR = 3.7$; $n = 896$) after controlling for severity of disease (Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002). These previous studies did not measure inflammatory proteins or control adequately for clinical or demographic variables.

This finding that depression was of greater significance in MACE prediction when inflammatory proteins were removed from the analysis suggests that inflammatory proteins may be partial mediators of depression on MACE. Depression may lead to MACE by increasing levels of inflammatory proteins or by other causal pathways. Whether depression causes or results in increased levels of inflammatory proteins remains unknown. The mechanisms that underlie this depression-related increase in inflammatory proteins are not well understood. Nevertheless, our study indicates that depression is a significant risk factor for MACE, even after adjusting for levels of inflammatory proteins and traditional and clinical risk factors.

One strength of our study is that our patients represent those seen in clinical practice where stents are placed in different-sized arteries in different locations, unlike patients in clinical trials where stents are usually inserted in new lesions in large arteries. The fact that ours is a prospective study and the clinical and morphological aspects of our population were well defined also provides strength. Another strength of this study is our ability to control for confounders of MACE through the use of an extensive database of clinical variables and exclusion criteria that controlled for physical causes of increased levels of inflammatory proteins.

Although a strength in some ways, our real-world clinical setting is also a limitation because of variations in intervention techniques and in the clinicians conducting the interventions. Another limitation is the use of a 1-question screening tool for assessing depression and the

time period (e.g., 1 year preceding PCI). Although one might anticipate that there would be more depression before a major coronary intervention, we are reassured that only 20% of the patients screened positively for depression; therefore, it is not a matter of very large numbers of patients answering the question positively. This 20% also included patients who may have had major depression. We recognize that the use of a validated depression scale would probably be more meaningful in this situation. Nevertheless, depression, as measured by our single question, appears to be clinically important in the relationship between depression and MACE. A similar question was used to screen for depression in cardiovascular patients in the INTERHEART study, which found that patients admitted to the coronary care unit with MI were more likely than those in a control group to answer yes to a question that asks about feeling sad, blue, or depressed for 2 weeks or more in a row during the past 12 months (Rosengren et al., 2004).

Our findings regarding depression and inflammatory proteins have implications for future research and treatment. If inflammatory proteins mediate depression and MACE, then treatment of depression may be aimed at reducing levels of inflammatory proteins. The independent effects of depression beyond that of inflammatory proteins suggest depression also influences MACE through other pathways. Thus, decreasing future MACE in patients may depend on treating depression and reducing inflammatory protein levels.

The current study should be repeated in other cardiovascular populations using a validated depression screening tool. Individuals differ greatly with respect to inflammatory protein levels during coronary events. Genetic factors may be involved in the variation of inflammatory proteins because inflammatory protein levels vary considerably among patients. Research suggests a relationship between genetic polymorphisms and inflammatory protein levels. The findings in this study suggest that inflammatory proteins mediate the relationship between depression and MACE. Future research is needed in cardiovascular patients undergoing physical or psychological factors that initiate temporal inflammatory protein elevations; these findings would increase our understanding of the biobehavioral mechanisms that link depression, inflammation, and subsequent coronary events in patients with cardiac disease. Moreover, this line of research could provide the rationale for testing environmental triggers of depression and the effects of depression interventions on inflammatory proteins in this population. Such information could ultimately allow the development of interventions to decrease MACE in this population.

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References

- Albus C, Jordan J, Herrmann-Lingen C. Screening for psychosocial risk factors in patients with coronary heart disease-recommendations for clinical practice. *European Journal of Cardiovascular Prevention and Rehabilitation* 2004;11:75–79. [PubMed: 15167210]
- Angiolillo DJ, Biasucci LM, Liuzzo G, Crea F. Inflammation in acute coronary syndromes: Mechanisms and clinical implications. *Revista Española de Cardiología* 2004;57:433–446.
- Blankenberg S, Rupprecht HJ, Bickel C, Peetz D, Hafner G, Tiret L, et al. Circulating cell adhesion molecules and death in patients with coronary artery disease. *Circulation* 2001;104:1336–1342. [PubMed: 11560847]

- Bunker SJ, Colquhoun DM, Esler MD, Hickie IB, Hunt D, Jelinek VM, et al. "Stress" and coronary heart disease: Psychosocial risk factors. *Medical Journal of Australia* 2003;178:272–276. [PubMed: 12633484]
- D'Agostino RB, Kannel WB, Belanger AJ, Sytkowski PA. Trends in CHD and risk factors at age 55–64 in the framingham study. *International Journal of Epidemiology* 1989;18(3 Suppl 1):S67–S72. [PubMed: 2807709]
- Danner M, Kasl SV, Abramson JL, Vaccarino V. Association between depression and elevated c-reactive protein. *Psychosomatic Medicine* 2003;65:347–356. [PubMed: 12764206]
- Frasere-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *Journal of the American Medical Association* 1993;270:1819–1825. [PubMed: 8411525]
- Frasere-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation* 1995;91:999–1005. [PubMed: 7531624]
- Galis ZS, Sukhova GK, Kranszhofer R, Clark S, Libby P. Macrophage foam cells from experimental atheroma constitutively produce matrix-degrading proteinases. *Proceedings of the National Academy of Sciences of the United States of America* 1995;92:402–406. [PubMed: 7831299]
- Gaspardone A, Crea F, Versaci F, Tomai F, Pellegrino A, Chiariello L, et al. Predictive value of c-reactive protein after successful coronary artery stenting in patients with stable angina. *American Journal of Cardiology* 1998;82:515–518. [PubMed: 9723643]
- Gidron Y, Gilutz H, Berger R, Huleihel M. Molecular and cellular interface between behavior and acute coronary syndromes. *Cardiovascular Research* 2002;56:15–21. [PubMed: 12237162]
- Gogo PB Jr, Schneider DJ, Watkins MW, Terrien EF, Sobel BE, Dauerman HL. Systemic inflammation after drug-eluting stent placement. *Journal of Thrombosis and Thrombolysis* 2005;19:87–92. [PubMed: 16052297]
- Gomma AH, Hirschfield GM, Gallimore JR Jr, Lowe GD, Pepys MB, Fox KM. Preprocedural inflammatory markers do not predict restenosis after successful coronary stenting. *American Heart Journal* 2004;147:1071–1077. [PubMed: 15199358]
- Group, NW. Assessment and treatment of depression in patients with cardiovascular disease. Bethesda, MD: National Institutes of Health; 2005.
- Kini AS, Lee PC, Mitre CA, Kim MC, Kamran M, Duffy ME, et al. Prediction of outcome after percutaneous coronary intervention for the acute coronary syndrome. *American Journal of Medicine* 2003;115:708–714. [PubMed: 14693323]
- Kozinski M, Krzewina-Kowalska A, Kubica J, Zbikowska-Gotz M, Dymek G, Piasecki R, et al. Percutaneous coronary intervention triggers a systemic inflammatory response in patients treated for in-stent restenosis—comparison with stable and unstable angina. *Inflammation Research* 2005;54:187–193. [PubMed: 15953990]
- Kulick DL, Rahimtoola SH. Risk stratification in survivors of acute myocardial infarction: Routine cardiac catheterization and angiography is a reasonable approach in most patients. *American Heart Journal* 1991;121(2 Pt 1):641–656. [PubMed: 1990780]
- Lesperance F, Frasere-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation* 2002;105:1049–1053. [PubMed: 11877353]
- Lesperance F, Frasere-Smith N, Theroux P, Irwin M. The association between major depression and levels of soluble intercellular adhesion molecule 1, interleukin-6, and c-reactive protein in patients with recent acute coronary syndromes. *American Journal of Psychiatry* 2004;161:271–277. [PubMed: 14754776]
- Liuzzo G, Buffon A, Biasucci LM, Gallimore JR, Caligiuri G, Vitelli A, et al. Enhanced inflammatory response to coronary angioplasty in patients with severe unstable angina. *Circulation* 1998;98:2370–2376. [PubMed: 9832480]
- Mann DL. Stress-activated cytokines and the heart: From adaptation to maladaptation. *Annual Review of Physiology* 2003;65:81–101.
- Mortensen RF. C-reactive protein, inflammation, and innate immunity. *Immunologic Research* 2001;24:163–176. [PubMed: 11594454]

- Moushmoush B, Kramer B, Hsieh AM, Klein LW. Does the AHA/ACC task force grading system predict outcome in multivessel coronary angioplasty? *Catheterization and Cardiovascular Diagnosis* 1992;27:97–105. [PubMed: 1446343]
- Naqvi TZ, Hachamovitch R, Berman D, Buchbinder N, Kiat H, Shah PK. Does the presence and site of myocardial ischemia on perfusion scintigraphy predict the occurrence and site of future myocardial infarction in patients with stable coronary artery disease? *American Journal of Cardiology* 1997;79:1521–1524. [PubMed: 9185646]
- Nelken NA, Coughlin SR, Gordon D, Wilcox JN. Monocyte chemoattractant protein-1 in human atheromatous plaques. *Journal of Clinical Investigation* 1991;88:1121–1127. [PubMed: 1843454]
- Oshima S, Ogawa H, Hokimoto S, Nakamura S, Noda K, Saito T, et al. Plasma monocyte chemoattractant protein-1 antigen levels and the risk of restenosis after coronary stent implantation. *Japanese Circulation Journal* 2001;65:261–264. [PubMed: 11316119]
- Pasterkamp G, Falk E. Atherosclerotic plaque rupture: An overview. *Journal of Clinical and Basic Cardiology* 2000;3:81.
- Pearson TA. New tools for coronary risk assessment: What are their advantages and limitations? *Circulation* 2002;105:886–892. [PubMed: 11854132]
- Qi X, Li S, Li J. The prognostic value of il-8 for cardiac events and restenosis in patients with coronary heart diseases after percutaneous coronary intervention. *Japanese Heart Journal* 2003;44:623–632. [PubMed: 14587644]
- Raison CL, Capuron L, Miller AH. Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology* 2006;27:24–31. [PubMed: 16316783]
- Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *New England Journal of Medicine* 1997;336:973–979. [PubMed: 9077376]
- Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the interheart study): Case-control study. *Lancet* 2004;364:953–962. [PubMed: 15364186]
- Sanchez-Margalet V, Cubero JM, Martin-Romero C, Cubero J, Cruz-Fernandez JM, Goberna R. Inflammatory response to coronary stent implantation in patients with unstable angina. *Clinical Chemistry and Laboratory Medicine* 2002;40:769–774. [PubMed: 12392302]
- U.S. Preventive Services Task Force. Screening for depression: Recommendations and rationale. *Annals of Internal Medicine* 2002;136:760–764. [PubMed: 12020145]
- Watkins C, Daniels L, Jack C, Dickinson H, van Den Broek M. Accuracy of a single question in screening for depression in a cohort of patients after stroke: Comparative study. *British Medical Journal* 2001;323:1159. [PubMed: 11711407]
- Williams JW Jr, Mulrow CD, Kroenke K, Dhanda R, Badgett RG, Omori D, et al. Case-finding for depression in primary care: A randomized trial. *American Journal of Medicine* 1999;106:36–43. [PubMed: 10320115]
- Zairis MN, Ambrose JA, Manousakis SJ, Stefanidis AS, Papadaki OA, Bilianou HI, et al. The impact of plasma levels of c-reactive protein, lipoprotein (a) and homocysteine on the long-term prognosis after successful coronary stenting: The global evaluation of new events and restenosis after stent implantation study. *Journal of American College of Cardiology* 2002;40:1375–1382.

Figure 1.

Model for potential mechanisms for depression triggers of coronary plaque rupture. NOTE: CRP = C-reactive protein; HPA = hypothalamic-pituitary-adrenal; ICAM = intracellular adhesion molecule; IL-1 = interleukin 1; IL6 = interleukin 6; MCP-1 = monocyte chemoattractant protein 1; MMP = matrix metalloproteinase; TNF α = tumor necrosis factor alpha; VCAM = vascular

Table 1

Single Variable and Multivariate Association Between Selected Covariates and MACE

Variable	Total Sample, N (%)	Single Variable Hazard Ratio	p-value	Multivariate Hazard Ratio	p-value
Age		0.9979	.8495	0.9833	.2163
Gender					
Female	126 (26)	0.9823	.9444		
Male	354 (74)				
Race ^a					
White	374 (81)	0.5488	.0242	1.7515	.1053
Other	86 (19)				
Smoking status					
Current	57 (12)				
Ex-smoker	294 (61)	0.7718	.4627		
Never	129 (27)	1.1446	.7154		
History of CHF					
None	398 (82)				
Past history	17 (4)	1.0800	.8964		
Current	48 (10)	1.6922	.4245		
Both 1 & 2	17 (4)	1.2376	.7941		
History of angina ^a					
0 none					
1 I	207 (43)	0.9661	.9298		
2 II	47 (10)	0.9839	.9571		
3 III	91 (19)	0.7541	.3226		
4 IV	134 (28)	0.0000	.9999		
Prior MI					
Yes	119 (24)	0.590	.4423		
No	361 (76)				
Diabetes ^a					
Yes	144 (30)	2.9200	.0000	2.0269	.0156
No	330 (69)				

Variable	Total Sample, N (%)	Single Variable Hazard Ratio	p-value	Multivariate Hazard Ratio	p-value
Hypertension					
Yes	384 (80)	2.542	.1108	0.6679	.3272
No	96 (20)				
Hyperlipidemia					
Yes	357 (74)	0.716	.3974		
No	123 (26)				
Lesion type					
A	10 (2)	0.0000	.9984		
B	388 (81)	1.0748	.8124		
C	82 (17)				
Prior PCI in target lesion					
Yes	12 (3)	0.002	.9621		
No	468 (97)				
Number of vessels treated					
1	433 (90.2)	1.5208	.2159	1.6737	.2165
2	43 (9)				
3	4 (0.8)				
Number of stents					
1	441 (92)			0.6470	
2	37 (7.7)	0.4658	.1945		.4316
3	1				
4	1				
Postprocedure stenosis					
Yes	80 (17)	0.9891	.7100		
No	400 (83)				
Depression					
Yes	86 (20)	1.8107	.0183	1.8867	.0495
No	390 (80)				
No response	4 (0)				
hsCRP (mg/dL) ^a					
Norm 0.007–0.494					

Variable	Total Sample, N (%)	Single Variable Hazard Ratio	p-value	Multivariate Hazard Ratio	p-value
1. (<2)	125 (27)				
2. (2.00–4.80)	113 (24)	2.7624	.0077	2.9274	.0152
3. (4.81–11.8)	114 (24)	3.1906	.0019	2.5666	.0468
4. (>11.80)	115 (25)	2.4517	.0206	1.2190	.7020
ICAM (ng/mL) ^a					
Norm 115–306 ng/ml					
1. (<212.66)	117 (25)				
2. (212.66–253.57)	118 (25)	1.1057	.7880	1.0631	.8898
3. (253.58–315.46)	119 (25)	1.9066	.0616	1.3892	.4657
4. (>315.46)	116 (25)	1.9156	.0575	1.0994	.8438
TNF- α (pg/mL) ^a					
Norm ND–4.22 pg/mL					
1. (<0.78)	114 (25)				
2. (0.78–1.10)	117 (26)	2.2024	.0510	1.9995	.1136
3. (1.11–1.53)	111 (25)	2.5878	.0188	1.3715	.5050
4. (>1.53)	110 (24)	3.4816	.0012	1.1499	.7785
VCAM-1 (ng/mL) ^a					
Norm 395–714ng/mL					
1. (<471.76)	117 (25)				
2. (471.76–556.54)	101 (21)	2.0325	.0787	2.4307	.0830
3. (556.55–683.2)	136 (29)	2.5797	.0106	3.4765	.0080
4. (>683.23)	116 (25)	2.8309	.0055	2.3162	.1175
IL-6 pg/mL ^a					
Norm ND–12.5 pg/mL					
1. (<3.70)	116 (25)				
2. (3.70–6.09)	118 (25)	0.8795	.3687	1.7676	.1598
3. (6.10–10.47)	118 (25)	0.7692	.0677	0.8241	.6695
4. (>10.47)	118 (25)	0.6619	.0048	1.3778	.4939
E-selectins (ng/mL) ^a					
Norm 13–51.3 ng/ml					
1. (<26.46)	114 (25)				

Variable	Total Sample, N (%)	Single Variable Hazard Ratio	p-value	Multivariate Hazard Ratio	p-value
2. (26.46–36.64)	117 (26)	0.9147	.7948		
3. (36.65–54.05)	111 (25)	1.0794	.8169		
4. (>54.05)	110 (24)	1.2887	.4239		
MCP-1 (pg/mL) ^a					
Norm 72–295 pg/mL					
1. (<106.56)	118 (25)				
2. (106.56–150.64)	119 (25)	3.0830	.0042	4.1372	.0016
3. (150.65–223.39)	117 (25)	2.7012	.0133	3.0191	.0256
4. (>223.39)	115 (25)	3.0128	.0046	3.6356	.0164
MMP-1 (ng/mL) ^a					
Norm 0.179 - 1.00 ng/mL					
1. (<0.05)	100 (25)				
2. (0.05–0.15)	97 (25)	1.6255	.2515	1.6384	.2594
3. (0.16–0.46)	101 (26)	2.0812	.0192	2.1491	.0785
4. (>0.46)	95 (24)	2.3547	.0154	2.1853	.0594

NOTES: CHF = congestive heart failure; hsCRP = highly sensitive C-reactive protein; ICAM = intracellular adhesion molecule; IL-6 = interleukin-6; MCP-1 = monocyte chemoattractant protein; MI = myocardial infarction; MMP-1 = interstitial collagenase matrix metalloproteinase; PCI = percutaneous coronary intervention; TNF = tumor necrosis factor; VCAM-1 = vascular cell adhesion molecule-1.

^aTotal numbers do not add up to 480 because of missing data or insufficient sample quantity.